

# **Mortality in HIV and Tuberculosis patients following implementation of integrated HIV-TB treatment: Results from an open-label cluster-randomized trial**

## **SUPPLEMENTARY MATERIAL**

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## Statistical analysis

All analyses were performed according to the intention-to-treat principle. This analysis population consists of all patients newly diagnosed with (i) both TB and HIV (ii) HIV only (among patients previously treated for TB or those who never had TB before) and (iii) TB only (among patients already diagnosed with HIV or those who were never diagnosed with HIV) after QI implementation in the intervention arm or clinic enrolment in the control arm. No adjustments for multiple comparisons were carried out.

The demographic and clinical characteristics were summarized at an individual level and adjusted for clustering. At an individual level, descriptive summary measures were expressed as frequencies, and percentages for all variables, while the adjusted summaries were calculated as geometric means of cluster-specific proportions. Among HIV-TB co-infected patients, the timing of TB treatment or ART initiation was summarised and estimates not adjusted for clustering as inferential statistics were not drawn from these analyses.

Time at risk of death for each patient was calculated from the date of enrolment into care (which could be the date of HIV test, date of ART or TB treatment initiation, whichever occurred first), to either the date of patient death, transfer out, last clinic visit if lost-to-follow-up, or the month-12 cut-off date, whichever occurred first.

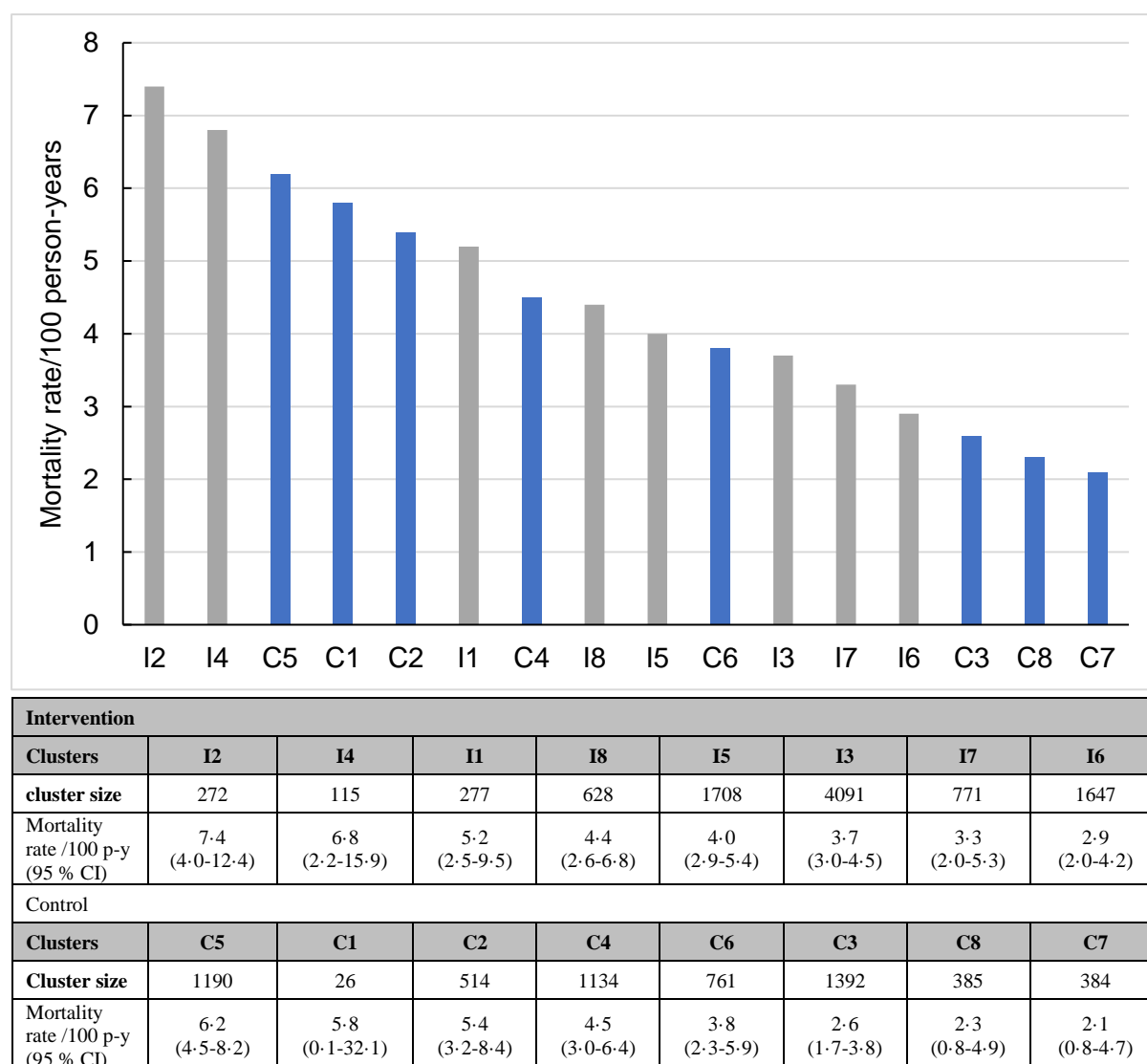
Mortality rate in each cluster was calculated as the number of patients who died, divided by the total number of person-years at risk of death. Thereafter, mortality rates in each of the intervention and control groups were calculated as geometric means of cluster-specific rates. Log cluster-specific mortality rates between study groups were compared using unpaired *t*-tests, with the confidence limits for mortality rates based on *t*-distribution. Mortality rate ratio (MRR), derived as a ratio of intervention to control groups mortality rates, was used to assess the effect of the intervention on mortality. Standard error for differences in log cluster-specific mortality rates between groups were obtained, and the 95% confidence interval from this standard error, using *t*-statistic with 14 degrees of freedom were calculated. The *t*-test is robust in analysing cluster randomised studies with small number of clusters. This method has its own limitations because it gives equal weight to each cluster, meanwhile the calculation of weights is not always recommended for studies with a small number of clusters due to possible inaccuracies in between-cluster variance.<sup>18</sup> However, due to huge variation in cluster sizes, we conducted a weighted cluster-level sensitivity analysis where optimal weights were calculated using the inverse variance method. A weighted *t*-test was used when comparing mortality rates between study arms.

A two-stage approach based on cluster level summaries was used to calculate an adjusted mortality rate ratio. The potential confounders such as age, gender, baseline CD4 count (for newly diagnosed HIV patients) and the municipality district where clusters are located were included in the model. Since not all patients are expected to have CD4 count measurements, we fitted one model with and the other without the CD4 count. In the first stage, we ignored the clustering at PHC supervisor level and used multivariable Poisson regression with all potential confounders included in the model except for the study arm, to obtain the ratio of observed to expected events (i.e., log-residuals) for each cluster. In the second stage, we compared the log-residuals between the study arms by calculating the geometric mean of the log-residuals in each arm and these were used in the derivation of the adjusted mortality rate ratio. Inferences were also based on *t*-distribution. This analytical approach described is recommended for cluster randomized trials with small (<15) number of clusters per arm.<sup>18</sup>

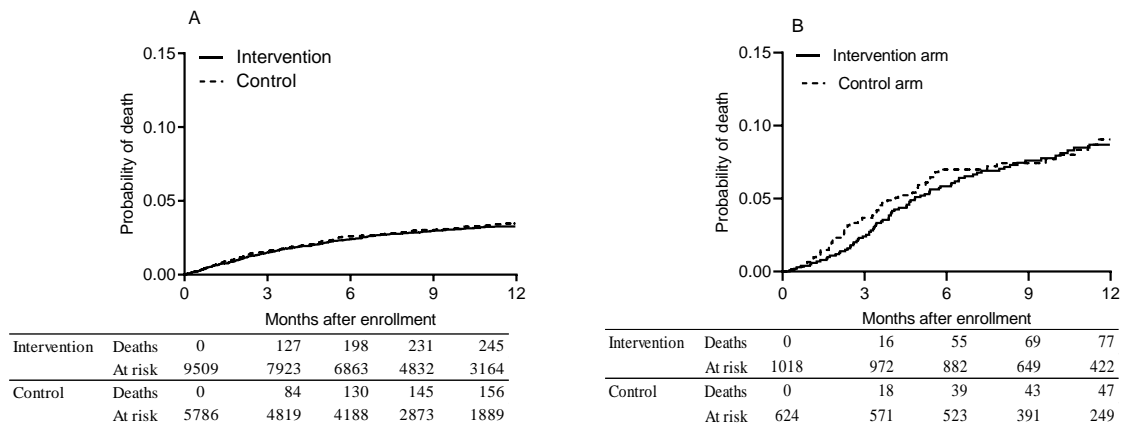
Even though individual-level regression methods are not robust for cluster randomized studies with fewer clusters, we conducted a secondary analysis using Cox proportional hazards regression with random effects (frailty models) to determine the effect of QI on mortality after adjusting for baseline characteristics. These models take clustering by PHC clinic supervisor into account through the random effects and adjust for age, sex, baseline CD4 count (for newly diagnosed PLWHA), and district.

Performance of HIV-TB process indicators at baseline and post-intensive phase in the intervention and control arms were calculated as follows: First, the proportions per cluster were calculated by summation of numerators divided by the sum of the denominators of all respective clinics in a cluster per month. A proportion of zero was replaced with 0.00001 (or 0.001 when using percentages). If a denominator was zero (i.e., no one was eligible), then that month was ignored. Second, we calculated cluster-specific geometric means (GM) across months associated with a phase. Third, study group-specific GM were calculated as cluster-specific proportions per phase.

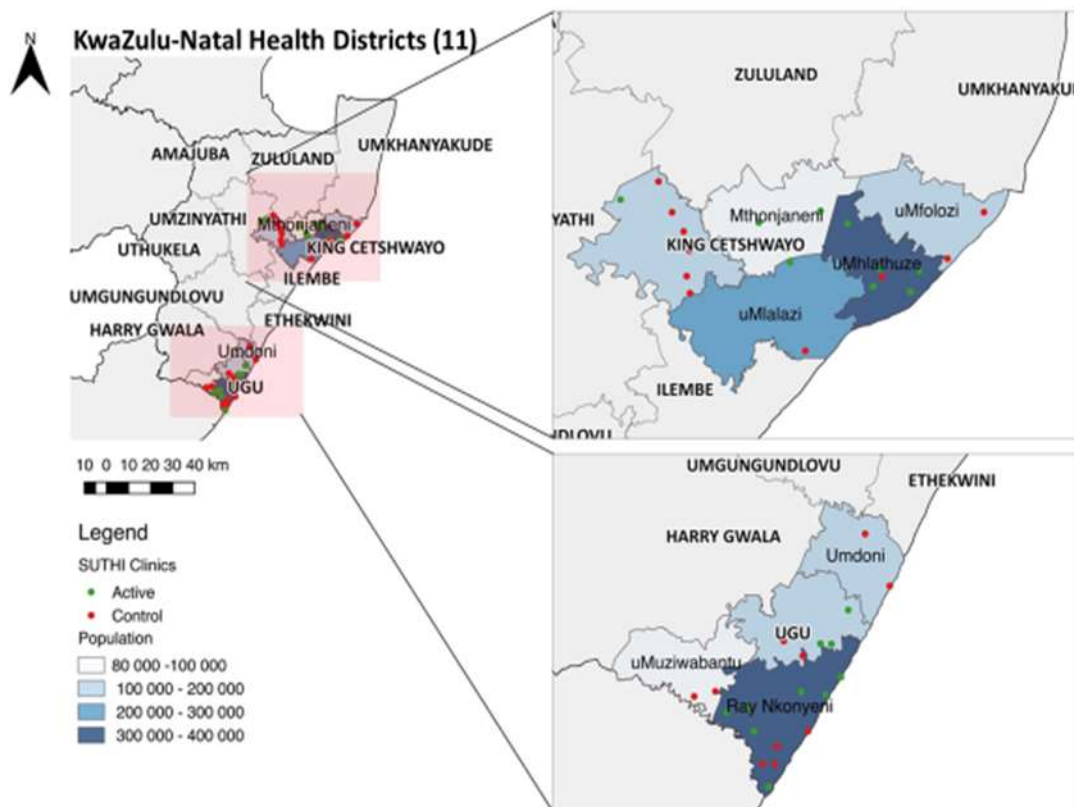
## Supplementary Tables and Figures



**Supplementary Figure 1: Cluster-specific mortality rates in the intervention (I) and control (C) arms among HIV-TB co-infected, PLWHA only and TB only patients. The grey and blue colour represents clusters in the intervention and control arm, respectively. CI: confidence interval, p-y: person-years**



**Supplementary Figure 2: Kaplan-Meier estimates of cumulative probability of death: (A) all patients; (B) HIV-TB co-infected patients**



**Supplementary Figure 3: SUTHI Primary healthcare clinics and population density**

**Supplementary Table 1: Baseline demographic and clinical characteristics of intervention and control arm patients enrolled in PHC clinics within 12 months and included in the analyses of the primary outcome**

Characteristics	Category	Intervention arm (N=9509)		Control arm (N=5786)	
		Unadjusted n(%)	Adjusted for clustering (%)	Unadjusted n(%)	Adjusted for clustering (%)
<b>Gender, n (%)</b>	Female	6078 (63.9%)	64.6%	3612 (62.4%)	62.4%
<b>Age (years), median (IQR)</b>		31 (25-39)	-	30 (24-38)	-
<b>Age group (years) at enrolment, n (%)</b>	≤15	235 (2.5%)	2.9%	233 (4.0%)	4.8%
	16 - 25	2211 (23.3%)	25.0%	1595 (27.6%)	27.4%
	26 - 35	3900 (41.0%)	38.0%	2145 (37.1%)	32.6%
	36 - 45	1943 (20.4%)	19.6%	1067 (18.4%)	18.7%
	> 45	1220 (12.8%)	13.6%	746 (12.9%)	13.7%
<b>Status, n (%)</b>	TB-HIV co-infected	1018 <sup>a</sup> (10.7%)	11.5%	624 <sup>a</sup> (10.8%)	11.1%
	TB positive	777 (8.2%)	7.6%	418 (7.2%)	8.2%
	HIV positive	7714 <sup>†</sup> (81.1%)	80.2%	4744 <sup>†</sup> (82.0%)	79.0%
<b>CD4 count (cells/μL) among newly diagnosed PLWHA<sup>†</sup></b>	<200	1341 (15.9%)	16.6%	838 (16.1%)	16.9%
	200-350	1243 (14.7%)	14.8%	825 (15.8%)	17.4%
	351-500	1146 (13.5%)	14.3%	682 (13.1%)	13.5%
	>500	1638 (19.4%)	19.0%	997 (19.1%)	21.8%
	Ineligible for CD4*	3055 (36.1%)	31.3%	1834 (35.2%)	25.2%
	Missing*	37 (0.4%)	0.5%	35 (0.7)	0.7%
<b>District, n (%)</b>	King Cetshwayo	5526 (58.1%)	-	2937 (50.8%)	-
	Ugu	3983 (41.9%)	-	2849 (49.2%)	-
<b>Area, n (%)</b>	Urban	5724 (60.2%)	-	1933 (33.4%)	-
	Rural	3785 (39.8%)	-	3853 (66.6%)	-

<sup>†</sup> Excludes 1195 TB positive patient with no record of HIV infection and 429 HIV-TB co-infected patients who were not newly diagnosed with HIV at enrolment (i.e., either tested positive for HIV or started ART more than 6 months before clinic enrolment)

\*Amongst those with absent or missing CD4 count (4 961): 55.7% are from urban area; 67.3% are females; 90.6% are between the ages of 16 and 49 and 55.0% are from KCD.

<sup>a</sup> 7 HIV-TB co-infected patients in the intervention arm and 10 in the control arm did not initiate ART.

<sup>†</sup> 145 PLWHA (people living with HIV/AIDS) only in the intervention arm and 129 in the control arm did not initiate ART

<sup>€</sup>Classification of clinics into urban and rural was from a pre-existing DoH classification received from the respective district office

IQR: interquartile range

**Supplementary Table 2: HIV-TB process indicator performance at baseline and post-intensive phase in the intervention and control arms**

HIV-TB Process indicators	Quality Improvement (QI) Group (%) (95% CI)	Standard of Care (SOC) Group (%) (95% CI)
<b>HIV Testing Services (HTS) for PHC clinic attendees</b>		
Baseline	84.8 (75.5-95.3)	85.3 (74.9-97.2)
Intensive phase	94.5 (91.9-97.1)	79.6 (68.7-92.3)
Within arm absolute change	9.7	-5.7
<b>HIV testing in TB patients</b>		
Baseline	88.7 (79.6-98.9)	85.7 (78.3-93.7)
Intensive phase	92.8 (88.3-97.4)	91.3 (87.1-95.7)
Within arm absolute change	4.1	5.6
<b>Screening for TB among PHC clinic attendees</b>		
Baseline	76.2 (65.4-88.9)	78.9 (68.3-91.1)
Intensive phase	83.4 (76.5-90.9)	79.3 (70.1-89.8)
Within arm absolute change	7.2	0.4
<b>ART initiation among HIV-TB co-infected patients</b>		
Baseline	95.8 (93.3- 98.3)	98.9 (97.6-100.0)
Intensive phase	91.7 (86.3- 97.4)	95.5 (93.1-98.0)
Within arm absolute change	-4.1	-3.4
<b>Initiating Isoniazid Preventive Therapy (IPT) among eligible new ART patients</b>		
Baseline	15.9 (4.8-52.5)	27.7 (16.2-47.1)
Intensive phase	61.2 (50.6-74.1)	36.8 (22.8-59.4)
Within arm absolute change	45.3	9.1
<b>Viral load testing at month 12 after ART initiation</b>		
Baseline	61.4 (56.4-66.8)	57.5 (45.7-72.4)
Intensive phase	72.2 (65.0-80.1)	72.8 (66.4-79.8)
Within arm absolute change	10.8	15.3

CI: confidence interval

**Supplementary Table 3: Cluster-adjusted mortality rates in the intervention and control arm stratified by gender, age, district, location and CD4 count among TB-HIV co-infected, PLWHA only and TB only patients, p-y: person-years**

	Intervention arm			Control arm			
Characteristic	Number of patients	Deaths/ person-years	Mortality rate/ 100 p-y (95% CI)	Number of patients	Deaths/ person-years	Mortality rate/ 100 p-y (95% CI)	Mortality rate ratio p-y (95% CI)
<b>Gender</b>							
Male	3431	153 /2246.38	8.0 (5.3 – 11.9)	2174	96 /1441.51	6.6 (4.0 – 10.9)	1.20 (0.67 – 2.15)
Female	6078	92 /4159.76	2.4 (1.5 – 4.0)	3612	60 /2438.82	2.5 (1.3 – 4.8)	0.97 (0.47 – 2.02)
<b>Age group (years)</b>							
≤15	235	4 /152.55	9.2 (4.0 – 21.1)	233	5 /162.69	7.4 (3.5 – 15.6)	1.24 (0.45 – 3.41)
16 - 49	8443	176 /5692.37	3.2 (2.2 – 4.6)	5045	105 /3364.21	2.7 (1.2 – 6.1)	1.17 (0.52 – 2.62)
≥50	831	65 /561.21	13.9 (8.1 – 24.0)	508	46 /353.43	13.6 (8.4 – 21.9)	1.03 (0.53 – 1.98)
<b>District</b>							
Ugu	3983	96 /2633.23	3.7 (2.2 – 6.2)	2849	93 /1938.14	4.1 (1.9 – 8.6)	0.92 (0.62 – 1.36)
King Cetshwayo	5526	149 /3772.92	5.0 (3.2 – 7.8)	2937	63 /1942.18	3.5 (1.7 – 7.1)	1.43 (0.93 – 2.21)
<b>Location</b>							
Urban	5724	128 /3830.58	3.5 (2.3 – 5.4)	1933	26 /1351.47	2.0 (1.5 – 2.7)	1.77 (1.43 – 2.20)
Rural	3785	117 /2575.56	5.0 (3.7 – 6.8)	3853	130 /2528.86	4.9 (3.4 – 7.0)	1.02 (0.71 – 1.47)
<b>CD4 count (cells/μL)*</b>							
Absent CD4 count	3092	73 /1972.03	4.4 (2.5 – 7.7)	1869	36 /1188.82	6.7 (0.7 – 61.5)	0.66 (0.08 – 5.28)
CD4<200	1341	66 /978.52	7.0 (4.9 – 9.9)	838	48 /582.90	7.4 (3.9 – 14.2)	0.94 (0.48 – 1.83)
CD4 200-350	1243	13 /897.82	2.2 (1.1 – 4.3)	825	8 /609.43	2.3 (1.0 – 5.4)	0.95 (0.36 – 2.51)
CD4≤350	2584	79 /1876.34	4.2 (3.0 – 5.7)	1663	56 /1192.33	4.4 (2.5 – 7.6)	0.95 (0.53 – 1.67)
CD4 351-500	1146	10 /830.22	2.0 (0.9 – 4.1)	682	5 /480.46	1.7 (1.0 – 2.9)	1.13 (0.51 – 2.50)
CD4>500	1638	7 /1183.50	1.5 (0.7 – 3.5)	997	5 /706.98	1.8 (0.8 – 4.3)	0.85 (0.29 – 2.52)

\*Excludes HIV-TB co-infected patients who were not newly diagnosed with HIV at enrolment  
PLWHA: people living with HIV/AIDS; CI: confidence interval

**Supplementary Table 4: HIV-TB factors associated with mortality among HIV-TB co-infected patients under the ITT population**

Characteristic	Model without CD4 count aHR (95% CI)	Model with CD4 count aHR (95% CI)
Study arm (ref: Control arm)		
Intervention arm	0.92 (0.63-1.33)	1.02 (0.65-1.60)
Gender (ref: male)		
Female	0.69 (0.48-0.99)	0.73 (0.45-1.16)
Age at enrolment (years) (ref: ≥50)		
≤15	No estimate*	No estimate*
16-49	0.61 (0.39-0.95)	0.58 (0.32-1.05)
District (ref: King Cetshwayo)		
Ugu	0.74 (0.51-1.07)	0.58 (0.32-1.05)
CD4 count at enrolment (cells/μL) (ref: <200)	-	
≥200	-	0.43 (0.23-0.82)
Ineligible for CD4	-	0.88 (0.54-1.42)

\*No deaths in this age group. aHR: adjusted hazard ratio

**Supplementary Table 5: Crude case fatality rates summary grouped by demographic and clinical characteristics under the ITT population**

Demographic Characteristics	Category	Intervention (N=245 deaths)		Control (N=156 deaths)	
		Number of deaths (%)	Case fatality rate (%)	Number of deaths (%)	Case fatality rate (%)
Gender, n (%)	Female	92 (38%)	1.5%	60 (38%)	1.7%
	Male	153 (62%)	4.5%	96 (62%)	4.4%
Age group (years) at enrolment, n (%)	≤15	4 (2%)	1.7%	5 (3%)	2.1%
	16 - 25	16 (7%)	0.7%	11 (7%)	0.7%
	26 - 35	75 (31%)	1.9%	53 (34%)	2.5%
	36 - 45	65 (27%)	3.3%	28 (18%)	2.6%
	>45	85 (35%)	7.0%	59 (38%)	7.9%
Area, n (%)	Urban	128 (52%)	2.2%	26 (17%)	1.3%
	Rural	117 (48%)	3.1%	130 (83%)	3.4%
District, n (%)	Ugu	96 (39%)	2.4%	93 (60%)	3.3%
	King Cetshwayo	149 (61%)	2.7%	63 (40%)	2.1%
Status, n (%)	TB/HIV co-infected	77 (31%)	7.6%	48 (31%)	7.7%
	TB positive	49 (20%)	6.3%	36 (23%)	8.6%
	HIV positive	119 (49%)	1.5%	72 (46%)	1.5%
HIV-TB co-infected: Started TB	Yes	77 (100%)	7.6%	48 (100%)	7.7%
TB only: Started TB	Yes	49 (100%)	6.3%	36 (100%)	8.6%
Started ART, n (%)	No	9 (5%)	5.9%	5 (4%)	3.6%
	Yes	187 (95%)	2.2%	115 (96%)	2.2%
CD4 count (cells/μL) among PLWHA	<200	66 (39%)	4.9%	48 (47%)	5.7%
	200-350	13 (8%)	1.0%	8 (8%)	1.0%
	351-500	10 (6%)	0.9%	5 (5%)	0.7%
	>500	7 (4%)	0.4%	5 (5%)	0.5%
	Absent CD4 count	73 (43%)	2.4%	36 (35%)	1.9%
Virological suppression (% with viral load < 1000 copies/ml)	Yes	108 (87%)	1.8%	77 (90%)	2.1%
	No	16 (13%)	2.2%	9 (10%)	2.0%

\* Excludes TB positive patient with no record of HIV infection and HIV-TB co-infected patients who were not newly diagnosed with HIV at enrolment (i.e., either tested positive for HIV or started ART more than 6 months before clinic enrolment).

**Supplementary Table 6: Number of clinics per cluster**

<b>Intervention</b>								
Cluster number	I1	I2	I3	I4	I5	I6	I7	I8
Number of clinics	1	1	4	1	3	3	3	4
<b>Control</b>								
Cluster number	C1	C2	C3	C4	C5	C6	C7	C8
Number of clinics	1	2	3	5	4	2	2	1